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The method for prediction of high-grade premature ventricular contractions in patients with heart failure and preserved ejection fraction

Aim	To develop a method for prediction of high-grade ventricular extrasystole (VE) in patients with chronic heart failure with preserved ejection fraction (CHF-PEF) based on results of an echocardiography (EchoCG) study.
Material and methods	At the first step, the study included 121 patients of the Cardiology Department, Municipal Clinical Hospital #31, St. Petersburg (calculation group) with symptoms and clinical signs of CHF-PEF (median age, 62 years). For testing accuracy of the developed formula, a control group was formed, which consisted of 42 patients with CHF-PEF (median age, 59 years). EchoCG at rest and ECG Holter monitoring were performed for all patient. The VE classification according to B. Lown and M. Wolf (1971) in the M. Ryan (1975) modification was used. Results of the evaluation were determined by the most significant recorded grade. Grade III or higher VE were considered as high-grade VE.
Results	Using logistic regression analysis of data for patients of the calculation group, a statistical model was constructed and a respective formula was developed to predict a probability of high-grade VE in CHF-PEF patients depending on the presence of risk factors (EchoCG criteria). According to the obtained data the following factors primarily contributed to the model: interventricular septal (IVS) thickness (p=0.007; Wald=7.44), end-diastolic volume index (EDVI) (p=0.044; Wald=4.13), and the degree of diastolic dysfunction (DD) (p<0.0001; Wald=19.90). For testing the formula accuracy, the analysis was performed in the control group. Based on data of both stages, the following values were obtained: for the calculation group, the method sensitivity was 77.8%, the specificity was 82.4%, the accuracy was 81.0%; for the control group, 81.8%, 70%, and 76.2%, respectively; for both groups together, 79.3%, 80.0%, and 79.8%, respectively. In ROC-analysis of this prognostic model, the area under the ROC-curve (AUC) was 0.852 (95% CI: 0.776–0.910; p<0.0001) for the calculation group; 0.818 (95% CI: 0.669–0.920; p<0.0001) for the control group; and 0.855 (95% CI: 0.792–0.905; p<0.0001) for both groups together, which indicated a good quality of the prognostic model.
Conclusion	The EchoCG predictors of high-grade VE in patients with CHF-PEF included degree of DD, EDVI, and IVS thickness. The developed method with the constructed formula for prediction of high-grade VE in CHF-PEF patients showed high sensitivity, specificity and accuracy.

Keywords	Heart failure with preserved ejection fraction; sudden cardiac death; heart rhythm disorders; ventricular extrasystole; prediction
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Half of patients with chronic heart failure (CHF) have a left ventricular ejection fraction (LVEF) of more than 50% [1, 2]. The use of implantable cardioverter defibrillators to prevent life-threatening ventricular arrhythmias (VAs) along with various groups of modern medicines have increased survival rates in CHF with reduced LVEF. However, the prognosis for patients with CHF with preserved LVFV (HFpEF) did not change significantly in studies supporting the positive effects of the treatments on reduced LVEF CHF mortality [3]. According to the results of the meta-analyses of prospective studies, up to 32.1% of patients suffering from CHF with preserved LVEF die within a 4-year follow-up period [4].

Stratification of the risk of sudden cardiac death (SCD), which occurs in one of four patients with HFpEF, remains a pressing issue [5–7]. The significant role of life-threatening VAs in the origin of deaths of patients with reduced EF is well known [8, 9], but the mechanisms of SCD in patients with HFpEF are not well understood [10]. There are only experimental findings confirming the association

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between SCD and VAs in HFpEF [11]. The prevalence of this mechanism of SCD is expected to be confirmed after the completion of the ongoing trial VIP-HF (Ventricular Tachyarrhythmia Detection by Implantable Loop Recording in Patients with Heart failure with Preserved Ejection Fraction, NCT01989299), in which implantable looped recorders are used to examine the rate of VAs in patients with HFpEF and high risk of arrhythmic death.

The presence of diastolic dysfunction (DD) and morphological changes in the left heart accompanying HFpEF creates conditions for the development of irregular heart rhythms. LV fibrosis and hypertrophy contributing to the development of DD causes electrical remodeling of the myocardium and, consequently, the onset of VAs [12]. The presence of hypertrophy and dilation of the LV and its DD is associated with a higher incidence of VAs and higher-grade premature ventricular contractions (PVCs) [13–15]. Numerous studies showed the high prognostic significance of high-grade PVCs according to the Lown and Wolf classification (1971) as modified by Ryan (1975) (polymorphic coupled PVCs and unstable episodes of ventricular tachycardia) both in patients without structural changes of the heart and patients with LV hypertrophy and CHF. The presence of these variants of VAs is associated with a higher rate of hospitalizations and the risk of death, onset or deterioration of CHF [16–18].

Holter electrocardiographic (ECG) monitoring to detect prognostically unfavorable variants of VAs in patients with CHF, including with preserved EF, is recommended only in cases of heart palpitations or other symptoms suggestive of arrhythmias. However, rhythm disorders are often not accompanied by clinically relevant symptoms. Unlike Holter ECG monitoring, an echocardiographic examination should be performed in all patients with CHF to assess cardiac structure and function (recommendation class 1, evidence level C) [19]. In addition to defining structural and functional characteristics of the heart, echocardiography reveals the predictors of high-grade PVCs. Thus, the echocardiographic findings in patients with HFpEF can be used as a basis for the formation of a group of patients at high risk of SCD. They require careful observation, Holter ECG monitoring, other supplementary examinations, and possibly antiarrhythmic therapy.

Objective

Develop a method of prognosis of high-grade PVCs in patients with HFpEF based on echocardiographic findings.

Materials and Methods

At the first stage, 121 patients (prognosis group) with clinical symptoms and signs of HFpEF were included in the cross-sectional trial, including 96 (79.3%) female and 25 (20.7%) male patients. The median age was 62 (58; 69) years. Later, a control group was formed to verify the accuracy of the formula, which comprised 42 patients with HFpEF, including 33 (78.6%) female and 9 (21.4%) male patients. The median age was 59 years. Patients were enrolled for the trial during the scheduled inpatient treatment in the heart disease department of St. Petersburg City Clinical Hospital No. 31. HFpEF was diagnosed according to the Russian National Guidelines of the Russian Society of Heart Failure Specialists (OSSN), Russian Society of Cardiology (RKO), and Russian Scientific Medical Society of Primary Care Physicians (RNMOT) [19]. At least 50% EF measured by the Simpson method was used as a criterion for preserved EF. The exclusion criteria were: the presence of the permanent and persistent forms of atrial fibrillation; history of myocardial infarction; hemodynamically significant heart valve defects (moderate to severe); chronic obstructive pulmonary disease and/or bronchial asthma, and lack of informed consent.

All patients underwent a 6-minute walk distance (6MWD) test to identify a functional class (FC) of CHF along with echocardiography and 24-hour Holter ECG monitoring.

Echocardiography was carried out at rest using a Vivid 4 device (General Electric, USA). All measurements and calculations were made according to the Guideline of the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE) [20, 21]. Left ventricular mass (LVM) was calculated using the area-length formula. Left ventricular mass index (LVMI), left atrial volume index (LAVI) and left ventricular end-diastolic volume index (LVEDVI) were calculated. Pulmonary artery systolic pressure (PASP) was considered equal to the sum of the maximum grade of tricuspid regurgitation in continuous-wave Doppler and the right atrial pressure was determined by the diameter of the inferior vena cava and its collapse. The transmitral flow was measured using pulsed-wave Doppler to assess LV diastolic function: peak early (E) and late (A) diastolic filling velocity, deceleration time (DT) of early diastolic filling, and E/A ratio at rest. Tissue Doppler analysis was used to evaluate septal and lateral early diastolic velocities (E'), and the E/E' ratio was calculated. Diastolic dysfunction was diagnosed if septal and lateral early diastolic velocities E' were less than 8 cm/s and 10 cm/s, respectively, and the calculated LAVI was elevated to 34 mL/m^2 or more. In the absence of these changes, normal diastolic function of LV was confirmed, and the DD was identified as zero grade. In the presence of DD, the following criteria were used to grade it: Grade 1 DD – E/A ratio is less than 0.8 and extension of DT more than 200 ms; grade 2 DD – E/A ratio is more than 0.8 but less

than 2, E/E' is more than 8; grade 3 DD – E/A is more than 2 and DT is less than 160 ms.

Holter ECG monitoring was performed using portable devices – Kardiotechnika-04–8 (M) (INCART, Russia). The Lown and Wolf classification (1971) as modified by Ryan (1975) was used to assess the detected VAs: Grade 0 – no PVCs within 24 hours of monitoring; grade 1 – less than 30 PVCs within an hour of monitoring; grade 3 – more than 30 PVCs within an hour of monitoring; grade 3 – polymorphic PVCs; grade 4a – coupled monomorphic PVCs; grade 4b – coupled polymorphic PVCs; grade 5 – unstable episodes of VT, three or more consecutive PVCs at the rate more than 100 per minute. The results of the assessment were defined by the highest grade registered. High-grade PVCs were reported as grade 3 or higher.

The data were statistically processed using Statistica v.8.0 for Windows (StatSoft, USA). The study objects were characterized using descriptive statistics methods. The findings are expressed as the mean and standard deviation (M ± SD) in case of normal distribution, and as the median (Me) and interquartile range (25th and 75th percentiles) – Me (LQ; UQ) – in case of non-normal distribution. The Kolmogorov-Smirnov method was used to verify the normality of the distribution. To assess the significance of intergroup differences depending on the distribution parameters, the Student's T-test and the Mann-Whitney U-test (for two groups) were used in case of normal and non-normal distributions, respectively. The statistical significance of relative indicators was estimated using a contingency table analysis and Pearson's χ^2 test. The intergroup differences were statistically significant at $p<0.05$.

A multivariate binary logistic regression analysis was performed to model the relationship between the echocardiographic parameters and cases of high-grade PVCs. The relative contribution of individual attributes to the development of high-grade PVCs was expressed by the Wald statistics. The regression equation was assessed using the stepwise inclusion of predictors, which ranks the attributes according to their contribution to the model. The percentage of correct reclassifications (accuracy) was used as a goodness-of-fit test for the real distribution of observations and prognosis of the probability of high-grade PVCs based on the logistic regression equation. The sensitivity and specificity of the model were also calculated.

Results

Patients of the prognosis group were divided into two subgroups depending on the presence or absence of high-grade PVCs. Subgroup 1 included 85 (70.2%) patients without high-grade PVCs. Subgroup 2 included 36 (29.8%) patients with high-grade PVCs.

As seen in Table 1, patient subgroups with or without high-grade PVCs were comparable using the major clinical parameters. Patients in subgroup 2 were a little older and had worse 6MWD results and higher CHF FC than patients in subgroup 1. However, these differences were not statistically significant. Patients in both groups used similar medicines.

Echocardiographic examinations of patients with high-grade PVCs showed higher values of several parameters than those of patients without high-grade PVCs (Table 2): EDV, EDVI, interventricular septal (ISC) thickness, LAV, LAVI, PASP, E/E', and DD grade. Mitral early diastolic velocity (mean E') in subgroup 2 was, by contrast, lower than in subgroup 1 ($p=0.005$).

The logistic regression analysis of the echocardiographic and Holter ECG monitoring data of the 121 patients in the prognosis group allowed the construction of a statistical model for the prognosis of high-grade PVCs in patients with HFpEF depending on the presence of risk factors (echocardiographic criteria) (Table 3).

Thus, statistically significant indicators for the prognosis of high-grade PVCs are IVS thickness (Wald=7.44; exp (B) = 1325.783; $p<0.01$), EDVI (Wald=4.13; exp (B) =1.06; $p<0.01$), and DD (Wald=19.90; exp (B) =5.26; $p<0.01$).

Based on the findings, a formula was derived to determine the probability of high-grade PVCs in patients with CHF:

$$P = \frac{\exp(-14.25 + (7.19) \times x + (0.06) \times y + (1.66) \times z)}{1+\exp(-14.25 + (7.19) \times x + (0.06) \times y + (1.66) \times z),}$$

where P is a prognostic coefficient of high-grade PVCs, x is the IVS thickness (cm), y is EDVI (mL/m^2) and z is a grade of LVDD. High-grade PVCs are predicted in patients with HFpEF with $p \geq 0.4$.

According to Holter ECG monitoring, in 28 (78%) of the 36 patients with high-grade PVCs, the prognostic coefficient was more than 0.4. Eight patients (22%) had an incorrect prognosis. Of the 85 patients without high-grade PVCs, high-grade PVCs were not predicted by the used method in 70 (82%) cases, and the prognosis was false-positive in 15 (18%) cases.

The second step was to verify the accuracy of the formula. A control group was formed for this purpose, which included 42 patients with HFpEF and clinical and functional characteristics comparable to those of patients in the prognosis group (Table 1).

In the control group, high-grade PVCs were diagnosed using Holter ECG monitoring in 22 (52%) patients, of whom 18 (82%) had a correct prognosis made using the developed method. No high-grade PVCs were identified in 20 (48%) patients, and they were not predicted in 14 (70%) cases. The prognosis was false-positive in 6 (30%) cases.

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Table 1. Main clinical and functional characteristics of patients of the prognosis group and the control group

Parameter	Prognosis group				Control group, n=42	p_2
	Subgroup 1, n=85	Subgroup 2, n=36	p_1	Total, n=121		
Age, years	62 (58; 66)	66 (59; 73)	0.19	62 (58; 69)	59 (55; 67)	0.19
Female, n (%)	68 (80)	28 (77.8)	0.78	96 (79.3)	33 (78.6)	0.92
CAD, n (%)	45 (52.9)	20 (55.6)	0.79	65 (53.7)	19 (45.2)	0.34
Essential hypertension, n (%)	85 (100)	36 (100)	1.00	121 (100)	42 (100)	1.00
BMI, kg/m^2	31.8±5.1	31.2±5.5	0.56	31.6±5.2	31.8±4.5	0.81
CHF NYHA FC, class	1 (1; 2)	2 (1; 2)	0.08	1 (1; 2)	1 (1; 2)	0.28
6MWD	440.6±70.2	423.7±95.5	0.28	435.5±78.6	422.4±59.0	0.32
Complaints of irregular heartbeat, n (%)	46 (54.1)	23 (63.9)	0.32	69 (57.0)	23 (54.8)	0.80
LVEF, %	62.9±3.3	62.8±3.8	0.93	62.9±3.4	62.9±3.0	0.96

CAD, coronary artery disease; HHD, hypertensive heart disease; BMI, body mass index;
CHF FC, functional class of chronic heart failure; 6MWD, 6-minute walk distance; LVEF, left ventricular ejection fraction;
p_1, differences between subgroups 1 and 2; p_2, differences between the prognosis group and the control group.

Figure 1. ROC curve analysis, prognosis group. AUC=0.852

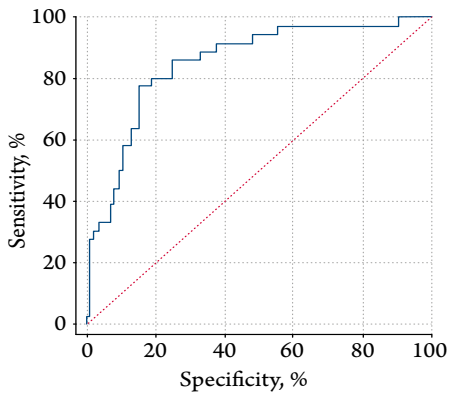

Figure 2. ROC curve analysis, control group. AUC=0.818

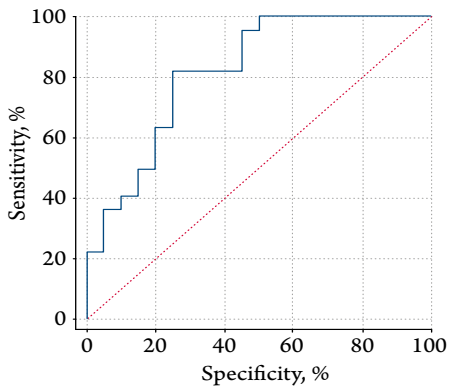

Figure 3. AROC curve analysis, prognosis, and control groups. AUC=0.855

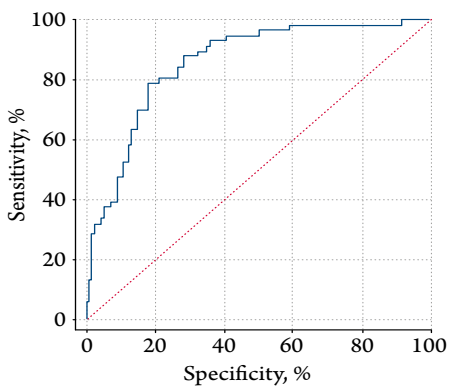

Table 2. Echocardiographic parameters for patients with high-grade PVC and without PVC

Parameter	Subgroup 1, n=85	Subgroup 2, n=36	p
EDV, mL	96.2±20.5	106.1±21.0	0.02
EDVI, mL/m^2	50.6±8.7	55.90±9.13	0.003
LVM, g	196.3±35.1	206.0±41.8	0.19
LVMI, g/m^2	103.7±15.9	108.5±18.2	0.15
IVS thickness, cm	1.12 (1.05; 1.21)	1.20 (1.10; 1.25)	0.009
LAV, mL	62.2±13.9	70.2±16.4	0.007
LAVI, mL/m^2	32.8±6.3	37.0±7.5	0.002
PASP, mm Hg	27.0 (25.0; 32.0)	32.0 (30.0; 35.0)	0.0003
E, m/s	0.68±0.16	0.71±0.16	0.38
A, m/s	0.85±0.13	0.87±0.16	0.47
E/A	0.79 (0.71; 0.88)	0.83 (0.71; 0.93)	0.51
E', cm/s	8.5 (7.5; 9.5)	7.8 (7.0; 8.8)	0.005
E/E'	8.04±2.05	9.01±1.55	0.01
DD grade	0 (0; 1)	2 (1; 2)	<0.00001

EDV, end-diastolic volume; EDVI, end-diastolic volume index;
LVM, left ventricular mass; LVMI, left ventricular mass index;
IVS, interventricular septum; LAV, left atrial volume;
LAVI, left atrial volume index; PASP, pulmonary artery systolic pressure;
E, peak early diastolic filling velocity; A, peak late diastolic filling velocity;
E', mitral early diastolic velocity; DD, diastolic dysfunction.

Table 3. Logistic regression model for prognosis of high-grade PVC in patients with HFpEF (χ^2=43.250, p<0.001)

Parameter	Const.B0	IVS	EDVI	DD grade
Factor	-14.25	7.19	0.06	1.66
Standard error	3.62	2.64	0.03	0.37
p	0.0001	0.007	0.04	0.00002
-95% CI	-21.42	1.97	0.01	0.92
+95% CI	-7.07	12.41	0.12	2.39
Wald χ^2	15.47	7.47	4.13	19.90
p	0.00008	0.006	0.04	0.00001
OR (units)	0.0000006	1325.78	1.06	5.26
-95% CI	0.0000000005	7.16	1.00	2.52
+95% CI	0.0008	245585.30	1.13	11.00
OR (ranks)	–	22.01	25.25	27.71
-95% CI	–	2.33	1.08	6.34
+95% CI	–	207.87	588.11	121.07

Const.B0, a regression constant;
IVS, interventricular septum; EDVI, end-diastolic volume index; DD, diastolic dysfunction; OR, odds ratio;
CI, confidence interval.

In the prognosis group, the sensitivity of the method was 77.8%, specificity was 82.4%, and accuracy was 81.0%; in the control group, 81.8%, 70%, and 76.2%, respectively. For both groups jointly, 79,3%, 80.0%, and 79.8%, respectively.

The ROC analysis of the model showed that the area under the ROC-curve (AUC) was 0.852 (95% CI: 0.776–0.910; p<0.0001) in the prognosis group, 0.818 (95% CI: 0.669–0.920; p<0.0001) in the control group, and 0.855 (95% CI: 0.792–0.905; p<0.0001) in both groups jointly, which demonstrated the high quality of the prognostic model (Figures 1–3).

Discussion

VAs are common in patients with HFpEF. Thus, ventricular heart rhythm disorders were detected in 39.7% of patients with this pathological syndrome, according to the EPOCH-O-CHN trial register [22]. Our study included 29.8% of patients with only grade 3–4 PVCs. This means that deterioration of CHF, increased number of hospitalizations, and a higher risk of death due to VAs can be predicted in almost one in three patients [16–18].

The appearance of PVCs can be caused by CHF or a factor contributing to its progression. Fibrosis, concentric hypertrophy, and LV remodeling resulting in the development of DD cause myocardial electrical remodeling (delayed electrical impulses, increased cardiomyocyte action potential durations, and early postdepolarization), thus contributing to the development of VAs [12]. On the other hand, several studies showed that frequent PVCs could disturb myocardial relaxation, were associated with increased LA dimension, and reduced mitral ring systolic velocities [23, 24]. Our findings confirm that patients with HFpEF and high-grade PVCs have signs of structural remodeling of the left heart chambers, such as increased EDV, EDVI, IVS thickness, LAV, and LAVI, elevated PASP, and diastolic disorders: reduced E', elevated E/E' and, thus, a higher DD grade.

The predictors of VAs and SCD in patients with reduced EF and patients with CHD were identified and well-studied. However, the problem of predicting life-threatening ventricular rhythm disorders in the setting of preserved EF is still unresolved. The following independent predictors of SCD in patients with HFpEF are described in the literature: age, male sex, concomitant type 2 diabetes mellitus, history of myocardial infarction, left bundle branch block, levels of natriuretic peptides, and duration of stays in hospital [25–27]. However, diagnostic tactics in patients with HFpEF do not rely on these clinical risk factors in most cases. This is because Holter ECG monitoring, which allows for the detection of VAs, is utilized only when arrhythmia-related symptoms are apparent [19].

Kuznetsov et al. described a prognostic method for high-grade VAs in patients with CHD [28, 29]. The authors examined patients included in the register of coronary angiography procedures who had preserved and reduced LVEF, and patients with a history of myocardial infarction. Patients with high-grade VAs had a lower LVEF. The reduction in LVEF was a statistically significant prognostic index for high-grade VAs, which was reflected in the formula for calculating its probability. The proposed mathematical model included not only EF but also such predictors of high-grade VAs as age and end-diastolic LV dimension. Other sources confirm that LV dilatation is a relevant risk factor of SCD in patients with CHD [30]. Our findings are consistent with the literature. EDVI is an independent predictor of high-grade PVCs in patients with HFpEF. The probability of high-grade PVCs is 6% higher if EDVI increases by 1 mL/m^2.

LV hypertrophy is another well-known risk factor of SCD in patients with cardiovascular diseases. LVMI is the most commonly used index of LV hypertrophy [31, 32]. At the same time, there is evidence that IVS thickness is a relevant independent risk factor of death in patients with CHD, even if LVM is normal [33]. According to our findings, a 0.01cm increase in IVS thickness results in a 13-fold increase in the probability of high-grade PVCs in patients with NSCF.

The use of E' and E/E' in characterizing diastolic function can also be used to predict adverse clinical outcomes in patients with HFpEF, such as cardiovascular death and urgent hospitalizations [34–36]. Our calculations confirmed the relevance of DD as a risk factor for the development of VAs: when DD in patients with HFpEF increases by one grade, the probability of high-grade PVCs increases fivefold.

Thus, the logistic regression analysis was used to construct a statistical model allowing a prognosis for high-grade PVCs in patients with HFpEF to be constructed based on DD grades, EDVI, and IVS thickness. The calculations confirmed the exceptional quality of the model with a sensitivity of 79.3%, a specificity of 80.0%, and an accuracy of 79.8%. In the real-world clinical practice, the model will help to identify patients upon whom it is reasonable to perform Holter ECG monitoring, even if they do not have irregular heartbeats or other symptoms caused by heart rhythm disorders.

Conclusions

Thus, DD, EDVI, and IVS thickness are echocardiographic predictors of high-grade PVCs in patients with HFpEF. The developed method for forming a prognosis of high-grade PVCs in patients with HFpEF using the derived formula is highly sensitive, specific, and accurate.

No conflict of interest is reported.

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